A computational biomarker of idiopathic generalized epilepsy from resting state EEG

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Summary

Epilepsy is one of the commonest serious neurological conditions. It is characterized by the tendency to have recurrent seizures, which arise against a backdrop of apparently normal brain activity. At present, clinical diagnosis relies on: (i) case history, which can be unreliable; (ii) observing transient abnormal activity during electroencephalography (EEG), which may not be present during clinical evaluation; (iii) if diagnostic uncertainty occurs, undertaking prolonged monitoring in an attempt to observe EEG abnormalities, which is costly. Herein, we describe the discovery and validation of an epilepsy biomarker based on computational analysis of a short segment of resting-state (inter-ictal) EEG. Our method utilizes a computer model of dynamic networks, where the network is inferred from the extent of synchrony between EEG channels (functional networks) and the normalized power spectrum of the clinical data. We optimize model parameters using a leave-one-out classification on a dataset comprising 30 people with idiopathic generalized epilepsy (IGE) and 38 normal controls. Applying this scheme to all 68 subjects we find 100% specificity at 56.7% sensitivity, and 100% sensitivity at 65.8% specificity. We believe this biomarker could readily provide additional support to the diagnostic process.

Introduction

At present a confirmed diagnosis of epilepsy is made through a case history and a positive EEG, confirming the presence of epileptiform discharges. However, a positive EEG occurs at best in only 60% of cases, resulting in diagnostic uncertainty for many people[1], with significant associated costs[2]. These costs predominantly result from additional longer-term EEG monitoring, repeated hospital admissions, as well as unnecessary prescription of anti-epilepsy drugs.

Idiopathic generalized epilepsy (IGE) is one of the main classes of epilepsy. In recent years, studies comparing cohorts of people with IGE and cohorts of healthy controls have shown statistically significant alterations at the group level when examining resting-state features of the EEG using power spectrum[3], functional networks[4] and a model-driven analysis of functional networks[5]. However, substantial overlap of these markers between groups may render the measurement unsuitable as a diagnostic test or biomarker[6] for any one individual. Our aim therefore is to assess the performance of each of these methods as a classifier that has three outcomes for each individual: unequivocally IGE, unequivocally normal, or uncertain. Such a classifier could be used as a screening test in a non-specialist primary care setting, as well as a diagnostic validation test in a specialist epilepsy setting. This would focus further medical investigation and resources on a smaller subgroup, producing efficiency gains and cost savings.

Methods

We studied data from 38 healthy controls and 30 people with IGE aged between 16 and 59. The individuals with IGE were *drug naïve* and recruited through clinics at St Thomas's Hospital. A diagnosis of epilepsy was confirmed in each case by an experienced epilepsy specialist through observation of typical generalized spike-wave (GSW) activity on EEG either spontaneously or

following hyperventilation or photic stimulation. For 10 of these people the diagnosis was confirmed following an initial routine EEG. For the remaining 20, diagnosis was confirmed following sleep-deprived or longer-term EEG monitoring (including sleep). Similar healthy control EEG was collected at King's College Hospital EEG department. Controls gave written informed consent and data collection was approved by King's College Hospital Research Ethics Committee (08/H0808/157). Under UK law, patient data collected during normal clinical routine and anonymized before research use may be used for research without additional consent; this procedure was reviewed and approved for this project by St Thomas's Hospital and King's College Hospital's Research and Development departments.

A trained clinical EEG technician identified a 20-second long, GSW and artifact free, segment of eyes-closed "resting state" EEG activity from the initial stage of the recordings from each participant. These data were band-pass filtered using a Butterworth filter between 0.5 and 70Hz, and band-stop filtered between 48 and 52Hz to remove power-line artifacts. Since signal amplitude may vary between individuals due to different anatomical features (such as the size and shape of the cranium) the data were normalized by dividing the power spectrum in each channel by the total power in the spectrum averaged across all channels. This normalized power preserves relative differences in power between channels. We then band-pass filtered the EEG segments into either the alpha (8-13Hz) or low alpha bands[7] (6-9Hz). For segments band-pass filtered in the low alpha band, we further inferred functional networks using the Phase-Locking Factor[8] (PLF) and phase-lags (as previously described)[5].

For the purpose of biomarker discovery, we consider measures that have demonstrated group-level differences between people with IGE and healthy controls using resting-state EEG. First, the peak in *alpha power* across occipital EEG channels, which is known to shift towards lower frequencies in people with IGE[3]. Second, the *mean-degree* of the PLF-inferred low alpha functional network,

which is elevated in people with IGE[4]. Third, a model-driven analysis where the low alpha functional network inferred from the EEG of each individual is integrated within a phase oscillator model (of Kuramoto type)[5]. Here the *local coupling* constant within each node of the network is inferred by multiplying the variance of the signal in the corresponding EEG channel by a uniform parameter *K*, to give a subject-specific dynamic network model of the brain. The seizure-generating capability of each region within this model is then evaluated computationally, as the average level of emergent seizure activity across the whole network driven by the region of interest (see Fig. 1A).

The performance of all three candidate biomarkers was evaluated using "leave-one-out" classification[9], in which all 30 people with IGE and 38 controls are pooled, the data from one subject is successively left aside and the remaining data used as the training set. In each case, thresholds are determined to give the highest sensitivity for 100% specificity and the highest specificity for 100% sensitivity in the training set. In turn, these thresholds are applied to classify the test subject as follows: If the value of local coupling is on the IGE side of both thresholds, then the individual is classified as unequivocally having epilepsy. The individual is classified as unequivocally normal if their value is on the control side of both thresholds. If their value lies between these thresholds they are classified as uncertain. A graphical representation of this approach is shown in Fig. 1B. Since each outcome is discrete and non-normal, we use the Friedman test[10] (non-parametric repeated measures ANOVA) to assess the relative performance of each biomarker.

Results

Successively optimizing the channel location and value of the local coupling constant to give the highest levels of sensitivity and specificity in each training set, the *local coupling* biomarker resulted in 56.7% sensitivity (given 100% specificity) and 65.8% specificity (given 100%

sensitivity). Specifically, 17 of 30 people with IGE were classified as unequivocally having epilepsy, 10 received an uncertain classification, and three were misclassified. Of the 38 healthy controls, 25 were correctly classified and 13 received an uncertain classification.

In contrast, average power of the EEG power spectrum and the mean degree of the inferred functional network performed poorly with low sensitivity and specificity. The peak in alpha power resulted in 0% sensitivity (given 100% specificity) and 0% specificity (given 100% sensitivity). It classified no people with IGE as having epilepsy, 29 were classified as uncertain, and one was misclassified. Of the 38 healthy controls, 0 were correctly classified, 37 received an uncertain classification and one was misclassified. Mean degree resulted in 3.3% sensitivity (given 100% specificity) and 15.8% specificity (given 100% sensitivity). It classified one person with IGE as having epilepsy, 28 were classified as uncertain, and one was misclassified. Of the 38 health controls, 6 were correctly classified, 31 received an uncertain classification and one was misclassified.

The Friedman test confirms that the classification results of the local coupling biomarker are statistically significant for people with IGE (chi-squared = 26.77, $p<0.001$) and controls (chi-squared = 22.83, $p<0.001$) in comparison to the other potential biomarkers. Using pairwise comparison, we show that the local coupling performs consistently better than either average power (IGE: chi-squared = 14.22, $p<0.001$; controls: chi-squared = 7.14, $p = 0.007$) or mean degree (IGE: chi-squared = 13.24, $p<0.001$; controls: chi-squared = 19.17, $p<0.001$).

Discussion

Herein we describe the comparative analysis of three candidate biomarkers of IGE using 20s segments of “resting-state” EEG from cohorts of drug-naïve people with IGE and age- and gender-

matched healthy controls. To our knowledge these three candidates are the only published methods to date that have shown statistically significant differences at the group level using "resting-state" EEG. The best performing algorithm, based upon a computer model of local and global brain networks, achieved nearly 60% sensitivity given 100% specificity and more than 60% specificity given 100% sensitivity. We assessed performance in this manner since an ideal screening test to use in a non-specialist setting needs 100% sensitivity to ensure all people with IGE are captured, but some false-positives are tolerable; whereas a decision support tool in the specialist setting needs 100% specificity to avoid false-positives, but less than perfect sensitivity can be compensated for by further expert-driven evaluation.

The use of routinely acquired EEG data, combined with minimal computational cost for evaluating the biomarker, makes this an attractive proposition from the perspective of clinical decision support. At present, the most time-consuming part is visual identification of "resting-state" EEG, which in our study was performed by a trained EEG technician. Automating this process, would permit delivery of a result in real-time (potentially whilst EEG was still being collected). A critical advantage of this method is that there is no requirement to observe epileptiform discharges in EEG to make a diagnosis, since the method relies only on brief segments of "resting-state" EEG. This yields the potential for a screening service to be offered in a non-specialist primary care environment, a resource-poor setting, or even using non-specialist EEG carried out in the patient's home.

Whilst these results are promising, it is important to note potential confounds that may limit the sensitivity and specificity achievable. Of note, cortical excitability (and by assumption seizure likelihood) is known to vary according to time of day; varying in response to both physiological factors and external stimuli[11]. It has very recently been shown that endocrine activity displays the strongest relationship with this circadian change[12]. In this study, most recordings were taken in the

late morning or early afternoon and we found no significant difference (Wilcoxon test: p=1, t-test: p=0.758) in the times when recordings were taken and whether a subject was correctly classified (mean time – 12:52 +/- 1:36) or not (mean time – 12:38 +/- 2:19).

The full code written in MATLAB[13] can be found online[14].

Disclosure

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